Drugs - Real World Outcomes (2016) 3:115–120
DOI 10.1007/s40801-016-0064-7

ORIGINAL RESEARCH ARTICLE

Lung Adenocarcinoma with Anaplastic Lymphoma Kinase (ALK) Rearrangement Presenting as Carcinoma of Unknown Primary Site: Recognition and Treatment Implications

John D. Hainsworth[1] · F. Anthony Greco[1]

Published online: 10 March 2016

Abstract

Background Molecular cancer classifier assays are being used with increasing frequency to predict tissue of origin and direct site-specific therapy for patients with carcinoma of unknown primary site (CUP).

Objective We postulated some CUP patients predicted to have non-small-cell lung cancer (NSCLC) by molecular cancer classifier assay may have anaplastic lymphoma kinase (ALK) rearranged tumors, and benefit from treatment with ALK inhibitors.

Methods We retrospectively reviewed CUP patients who had the 92-gene molecular cancer classifier assay (CancerTYPE ID; bioTheranostics, Inc.) performed on tumor biopsies to identify patients predicted to have NSCLC. Beginning in 2011, we have tested these patients for ALK rearrangements and epidermal growth factor receptor (EGFR) activating mutations, based on the proven therapeutic value of these targets in NSCLC. We identified CUP patients with predicted NSCLC who were subsequently found to have ALK rearrangements.

Results NSCLC was predicted by the molecular cancer classifier assay in 37 of 310 CUP patients. Twenty-one of these patients were tested for ALK rearrangements, and four had an EML4-ALK fusion gene detected. The diagnosis of lung cancer was strongly suggested in only one patient prior to molecular testing. One patient received ALK inhibitor treatment and has had prolonged benefit.

Conclusions We report on patients with lung adenocarcinoma and ALK rearrangements originally diagnosed as CUP who were identified using a molecular cancer classifier assay. Although ALK inhibitors treatment experience is limited, this newly identifiable group of lung cancer patients should be considered for therapy according to guidelines for stage IV ALK-positive NSCLC.

Key Points

Patients with carcinoma of unknown primary who were predicted to have NSCLC were subsequently found to have tumors with anaplastic lymphoma kinase (ALK) rearrangements.

One patient received treatment with ALK inhibitors and has had prolonged benefit.

This group of patients should be considered for stage IV ALK-positive NSCLC therapy.

1 Introduction

The identification of specific molecular abnormalities in individual tumors is integral to the management of patients with many cancer types. Comprehensive genomic profiling of tumors is becoming increasingly common, although the clinical relevance of many of the findings remains unclear. However, testing for specific molecular abnormalities in selected cancer types [e.g., human epidermal growth factor 2 (HER2) in breast cancer or gastric/gastroesophageal

✉ John D. Hainsworth
John.Hainsworth@scresearch.net

[1] Sarah Cannon Research Institute and Tennessee Oncology, PLLC, 3322 West End Avenue, Suite 900, Nashville, TN 37203, USA

cancer; Kirsten rat sarcoma viral oncogene (KRAS) in colorectal cancer; v-Raf murine sarcoma viral oncogene homolog B (BRAF) in melanoma; EGFR and ALK in non-small-cell lung cancer (NSCLC)] is already a standard part of clinical practice, since highly active agents are available for treatment of cancers with these abnormalities [1–6].

Molecular testing is also being incorporated into the management of patients with CUP. In patients with CUP, an anatomic primary site cannot be clinically identified, even though small primary cancers are present and are usually detectable at autopsy [7, 8]. Molecular cancer classifier assays, which detect patterns of gene expression specific to the tissue of origin, can be used on a tumor biopsy specimen to accurately predict the cancer type or the primary site in most patients with CUP [9–11]. Clinical data support the use of site-specific therapy based on these predictions, rather than traditional empiric chemotherapy [12–15]. If specific cancers such as breast, colorectal, gastric, melanoma, or NSCLC are predicted in CUP patients by molecular cancer classifier assays or immunohistochemical (IHC) staining patterns, it seems reasonable to evaluate these tumors for the same potentially actionable molecular abnormalities that would be analyzed in their counterparts with known primary sites. Identification of such abnormalities could lead to additional effective treatment options; however, very limited clinical data currently exist to validate this approach.

In this report, we detail the clinical and pathologic features of patients with CUP who were predicted to have adenocarcinoma of the lung by a molecular cancer classifier assay, and subsequently had ALK rearrangements detected by focused molecular testing.

2 Methods

In this retrospective study, we reviewed records of CUP patients who had been evaluated with the 92-gene RT-PCR molecular cancer classifier assay (CancerTYPE ID; BioTheranostics, Inc.) as part of their diagnostic evaluation. Patients were diagnosed with CUP if an anatomic primary site was not identified during the following clinical evaluation: complete medical history, physical examination, chemistry profile, complete blood counts, computed tomography (CT) scans of the chest/abdomen/pelvis, serum PSA level (men), mammograms (women), and further focused evaluation based on signs/symptoms at presentation. Routine pathologic evaluation of biopsy specimens from CUP patients included histologic examination and a battery of IHC stains (guided by the histology and clinical features). Since 2008, when our CUP research program began a systematic evaluation of molecular testing, we have also performed a molecular cancer classifier assay on the tumor biopsy specimens of most CUP patients.

The first goal of this review was to identify CUP patients seen since 2011 who were predicted to have NSCLC by the 92-gene molecular cancer classifier assay [9]. Next, we identified patients within this group whose cancers had ALK rearrangements identified by subsequent FISH testing. Since 2011, we have tested for EGFR-activating mutations and ALK rearrangements whenever feasible in CUP patients predicted to have NSCLC, following the demonstration that these molecular abnormalities are important therapeutic targets in NSCLC [5, 6].

In this report, we review the clinical and pathologic features of CUP patients who were predicted to have NSCLC and who were then found to have an ALK rearrangement.

3 Results

Between May 2011 and May 2015, we evaluated 310 CUP patients with the 92-gene molecular cancer classifier assay; 37 patients (12 %) were given the diagnosis of NSCLC. Biopsy specimens from 21 of these 37 patients were tested for ALK rearrangements and EGFR-activating mutations. None of the 21 biopsies had EGFR-activating mutations. The biopsies of four of 21 patients tested (19 %) had ALK rearrangements (all EML4-ALK). The case histories of these four patients are detailed below, and are summarized in Table 1.

3.1 Patient Number 1

This 45-year-old non-smoking African-American female developed superior vena cava syndrome and was found by chest CT scan to have large contiguous mediastinal and right hilar masses, and right pleural effusion. No lung lesion was seen. Bronchoscopy showed external bronchial compression but no endobronchial lesions. A mediastinoscopy showed a large mediastinal mass; biopsy revealed metastatic adenocarcinoma, signet ring type. IHC staining showed CK7+/CK20-; stains for TTF1, ER/PR, GCDFP, and CDX2 were negative. Since no lung masses were identified by bronchoscopy or chest CT, the patient was considered to have CUP, although the clinical presentation strongly suggested adenocarcinoma of the lung. Clinical evaluation for extrathoracic metastases revealed only a 3-cm left adrenal mass.

The patient received treatment with concurrent radiation therapy and chemotherapy (carboplatin/pemetrexed). The biopsy specimen was sent for the 92-gene molecular cancer classifier assay, which indicated the lung as the likely

Table 1 Clinical and pathologic features of carcinoma of unknown primary site (CUP) patients with molecular diagnosis of non-small-cell lung cancer (NSCLC) and anaplastic lymphoma kinase (ALK) rearrangements (EML4-ALK)

Patient #	Age (years)/gender	Sites of metastases	Bronchoscopy/CT chest	Histology	IHC stains	Molecular diagnosis	% probability of molecular diagnosis
1	43/female	Mediastinum, adrenal	No endobronchial lesions/no lung lesions	Adenocarcinoma, signet ring	CK7+/CK20−, TTF1−	Lung adenocarcinoma	90
2	52/male	Mediastinum	No endobronchial lesions/no lung lesions	Poorly differentiated carcinoma	CK7+/CK20−, TTF1−, HCG/PLAP focal+	Lung adenocarcinoma	77
3	26/female	Ovary, bone, mediastinal/supraclavicular nodes	Not done/no lung lesions	Adenocarcinoma, signet ring	CK7+/CK20−, ER/PR−	Lung adenocarcinoma	90
4	78/female	Bone, mesenteric nodes, gastric/colonic mucosa	Not done/no lung lesions	Poorly differentiated carcinoma	CK7+/CK20−, TTF1+ CD56−	Lung adenocarcinoma	62

CT computerized tomography, *CK* cytokeratin, *IHC* immunohistochemistry, *TTF* thyroid transcription factor, *HCG* human chorionic gonadotropin, *PLAP* placental alkaline phosphatase, *CD56* neural cell adhesion molecule

tissue of origin (90 % probability). Subsequent FISH testing showed an ALK rearrangement (EML4-ALK).

After completing radiation therapy, she was improved but had a large residual mediastinal mass. She began treatment on a clinical trial with the ALK inhibitor crizotinib. She had further regression of the mass, and did well until she had an isolated brain recurrence 30 months later. She underwent stereotactic radiosurgery, and continued ALK inhibitor clinical trial therapy with a next-generation ALK inhibitor (PF-06463922; Pfizer, Inc.). She has had no further progression during the last year of therapy, and is continuing treatment.

Comment This patient is the only one of the four patients identified who had clinical features (mediastinal/hilar masses) strongly suggestive of lung cancer, although no endobronchial lesions were observed at the time of bronchoscopy, and no discrete lung lesion was present on CT chest scans. However, the IHC staining (TTF1-) was atypical of lung adenocarcinoma. Lung adenocarcinomas with signet ring features have been associated with ALK translocations. She responded to treatment with ALK inhibitors, and continues to benefit after >40 months of treatment.

3.2 Patient Number 2

This 52-year-old White male developed cough, chest pain, and a right flank mass. He had previously smoked cigarettes, but had stopped 10 years previously. Physical examination showed a firm 5-cm right flank mass. Chest CT scan showed a 4-cm mediastinal mass, a 3.5-cm pleural-based mass, and a small right pleural effusion. The right flank mass was removed, and surprisingly showed blastomycosis infection, for which he received treatment for 1 year with itraconazole. The patient had clinical improvement, and radiologic findings resolved with the exception of the mediastinal mass, which slowly enlarged from 3 cm to 5 cm. Bronchoscopy and head/neck endoscopy showed no lesions.

The patient had resection of the mediastinal mass, as well as biopsy of multiple other mediastinal lymph nodes. The 5-cm mass showed metastatic poorly differentiated carcinoma; all other biopsies were negative. IHC studies included: CK7+/CK20−, TTF1−, human chorionic gonadotropin (HCG) focally positive, placental alkaline phosphatase (PLAP) focally positive. The pathology was reviewed at Indiana University, and additional IHC studies including human placental lactogen, calretinin, WT-1, and podoplanin were negative. The tumor histology and overall IHC staining pattern were not felt to be compatible with a germ cell tumor. Testicular ultrasound was negative. The patient therefore had CUP with a poorly differentiated carcinoma.

Biopsy tissue was sent for the 92-gene molecular cancer classifier assay, which predicted a diagnosis of lung adenocarcinoma (77 % probability). Subsequent FISH testing showed an ALK rearrangement (EML4-ALK).

Based on the prediction of lung cancer, adjuvant therapy with four courses of chemotherapy was recommended. However, the patient declined adjuvant therapy, and has now been followed for 36 months with no evidence of recurrence. Treatment with an ALK inhibitor will be recommended if he develops recurrence in the future.

Comment Although this patient had a mediastinal mass, no lung lesions were detected on CT scan, at bronchoscopy, or at thoracotomy. Immunohistochemistry was atypical for lung adenocarcinoma (TTF1-negative); focally positive HCG and PLAP stains raised the possibility of a germ cell tumor but further IHC stains and review by a genitourinary pathologist did not result in a precise diagnosis. Specific molecular testing for ALK rearrangement may not have been considered in the absence of the lung adenocarcinoma prediction by the molecular cancer classifier assay.

3.3 Patient Number 3

This 26-year-old White female nonsmoker developed right pelvic pain and was found to have a 6-cm cystic right ovarian mass. CT of the abdomen/pelvis showed no other lesions; serum tumor markers included CEA 43, AFP/HCG normal. She had a laparotomy with right oophorectomy, which revealed metastatic mucinous adenocarcinoma with signet ring pattern. Immunohistochemical staining included: CK7+, CK20−, ER/PR−, CD56 −, chromogranin−. Further clinical evaluation included normal chest CT, colonoscopy, upper gastrointestinal (UGI) endoscopy, and mammograms. Positron emission tomography (PET) scan showed abnormal uptake in the right eighth rib, a mediastinal node and a left supraclavicular node. The patient was given the diagnosis of CUP, with a gastrointestinal origin considered most likely.

She received six courses of paclitaxel and carboplatin, followed by local radiation therapy to the right eighth rib lesion (which had become symptomatic). She did well for 16 months, when she had recurrence in retroperitoneal lymph nodes. She also developed nephrotic syndrome, thought possibly to be paraneoplastic. Chest CT scan also showed a 1.6-cm subcarinal node, a small right hilar node, and several small indeterminate subpleural nodules in the left lung. Biopsy of a retroperitoneal node showed metastatic adenocarcinoma identical to the previous biopsy. A molecular cancer classifier assay diagnosed lung adenocarcinoma as the likely tissue of origin (90 % probability). In addition, an ALK rearrangement was detected (EML4-ALK).

At the time of these findings, the patient had already started second-line therapy with modified FOLFOX-6 + bevacizumab, to which she had an objective response (including resolution of her nephrotic syndrome). She has remained in remission following completion of treatment. If relapse occurs in the future, treatment with an ALK inhibitor will be considered.

Comment This young woman developed symptoms related to a Kruckenberg tumor, and was found to have metastatic adenocarcinoma (signet ring features). At presentation, she had no intrathoracic tumor identified; pathologic evaluation led to suspicion of a gastrointestinal site of origin. She had two unusually good responses to empiric therapy for CUP (paclitaxel/carboplatin and modified FOLFOX6 + bevacizumab, respectively), and remains in remission 44 months after completion of second-line therapy. The diagnosis of NSCLC was not strongly suggested by clinical or pathologic features; however, the mucin-producing, signet ring adenocarcinoma and her non-smoking status are consistent with ALK-rearranged lung cancer. Treatment with an ALK inhibitor has not yet been indicated.

3.4 Patient Number 4

This 78-year-old White female developed nausea, weight loss, and progressive abdominal distension. She had previously been a cigarette smoker, but had stopped smoking 30 years previously. Chest and abdominal CT scans showed enlarged mesenteric lymph nodes, a 1.4-cm pretracheal lymph node, and bone lesions (ribs, sternoclavicular joint). A core needle biopsy of the mesenteric node showed poorly differentiated carcinoma. IHC studies included AE1/AE3+, CK7+, CK20−, TTF1+. UGI endoscopy showed two malignant-appearing gastric ulcers, biopsy of which showed poorly differentiated carcinoma. Colonoscopy also showed a 2-cm ulcer in the transverse colon, biopsy positive for poorly differentiated carcinoma. These ulcers were most consistent with metastases to the epithelial surfaces. The clinical opinion was that the patient had CUP with poorly differentiated carcinoma.

Biopsy material was sent for a molecular cancer classifier assay, which resulted in a prediction of lung adenocarcinoma (62 % probability). Subsequent FISH testing showed ALK rearrangement (EML4-ALK). Unfortunately, the patient declined all treatment, including a trial of an ALK inhibitor, primarily due to her poor performance status. She was referred to hospice for symptomatic care.

Comment This elderly female with a distant history of smoking cigarettes had a presentation which did not suggest lung cancer. Predominant metastatic sites were in the abdomen (mesenteric nodes, stomach, colon) and bones. Although the TTF1 stain was positive, the unusual clinical

presentation and poorly differentiated histology did not allow a definitive diagnosis of metastatic lung cancer. However, the molecular cancer classifier diagnosis and the ALK rearrangement make an occult primary adenocarcinoma of the lung very likely.

4 Discussion

We describe several patients who had CUP following standard clinical and pathologic evaluations. In each case, a 92-gene molecular cancer classifier assay was performed, and predicted lung adenocarcinoma. The prediction of lung cancer resulted in further specific molecular testing and the identification of ALK rearrangements in each tumor. The patients presented in this report very likely had primary occult lung adenocarcinomas. The identification of ALK rearrangements in CUP patients diagnosed as lung adenocarcinoma by a molecular cancer classifier assay has not been previously reported.

Lung cancer has long been recognized as one of the most common cancer types identified in patients with CUP; in early autopsy series, occult lung primaries were found in 17–27 % of patients [8, 16]. More recently, NSCLC was predicted by the 92-gene molecular cancer classifier assay in 27 of 252 patients (11 %) evaluated and treated in a multicenter prospective study [12]. In our current review of 310 CUP patients, we found a similar percentage (12 %) of lung cancer predictions. The incidence of ALK rearrangements in CUP patients predicted to have NSCLC cannot be stated with certainty. Four of our 21 patients tested (19 %) had ALK rearrangements (seemingly higher than the 5 % incidence in patients with known NSCLC), but the small patient numbers preclude definitive conclusions. Also of interest is the fact that none of our 21 patients had EGFR-activating mutations, as compared to a 10 % incidence in patients with known NSCLC. Whether these findings indicate true differences between these populations or are related to the small sample size is unknown.

Without the prediction of the molecular cancer classifier assay, it is unlikely that the ALK rearrangements in these four tumors would have been identified. Only in Patient Number 1 were the clinical features highly suggestive of NSCLC, although no anatomic primary site was identified by chest CT scan or bronchoscopy. In the other three patients, the clinical presentations were not strongly suggestive of lung cancer (two patients had predominant intra-abdominal disease, and a third, who had a mediastinal mass, had no lung lesions detected). Likewise, the histologic examination and IHC staining batteries were highly suggestive of lung adenocarcinoma in only one case. In two patients, the TTF1 stain was negative (known to be positive in about 80 % of lung adenocarcinomas). In one patient, scattered focal staining for HCG and PLAP raised the possibility of a germ cell tumor, although this diagnosis was considered unlikely after expert review and additional IHC stains.

Since none of the patients had an anatomic primary site found in the lung, the molecular cancer classifier predictions cannot be unequivocally confirmed. However, it is of interest that the patients exhibited some of the features of ALK-positive NSCLC: All patients were either never smokers or had a distant smoking history, and two of the four patients had signet ring adenocarcinomas, found to be common in ALK-positive NSCLC [17, 18]. In addition, the specific ALK rearrangement (EML4-ALK) found in all four tumors is strongly associated with adenocarcinoma of the lung.

To date, only one of these four patients has received treatment with ALK inhibitors. This patient had a partial response to crizotinib, which persisted for 30 months before recurrence with an isolated brain metastasis. Following stereotactic radiotherapy, the patient was switched to an investigational ALK inhibitor, with ongoing disease stability after 12 additional months of treatment. Two of the other patients are currently disease-free after previous treatment, although both remain at risk for relapse. Treatment with ALK inhibitors is probable at the time of relapse.

Recently, the use of comprehensive molecular profiling to search for the presence of actionable genetic alterations has become much more widespread. Since the heterogeneous group of CUPs is known to include cancers arising from a diverse group of occult primary sites, and has previously been associated with a high number of mutations, it is predictable that some of these cancers will contain actionable mutations. In a group of CUPs in which comprehensive genomic profiling was performed, at least one molecular abnormality was identified in 192 of 200 tumors (96 %) [19]. Molecular alterations targeted by currently marketed anticancer drugs [HER2, EGFR, BRAF, ALK, rearranged during transfection proto-oncogene (RET)] were present in 23 %.

In the future, most treatment decisions may be based on the results of comprehensive screening for actionable molecular abnormalities, making the identification of the primary site (and the molecular cancer classifier assay) unnecessary. However, at present the use of both tests is advisable. Standard treatment for most cancer types still involves the use of specific regimens of chemotherapy (±targeted agents) derived empirically, and not guided by the identification of specific molecular abnormalities. In addition, clinical data regarding the response of CUP patients to therapy targeted at molecular abnormalities identified by screening remains limited [15, 20–22].

In this report, we document one CUP patient with an ALK rearrangement who had an excellent response to ALK inhibition. Additional studies of drugs directed or matched to a particular genetic alteration are underway in a variety of solid tumors, including CUP.

5 Conclusion

In this report, we describe a group of CUP patients with adenocarcinoma of the lung, who were predicted to have NSCLC by molecular cancer classifier assay; subsequent testing identified ALK rearrangements in each cancer. Although further clinical experience is needed, it is reasonable to follow guidelines for the treatment of ALK-positive lung adenocarcinoma when managing such patients.

Author contributions Both authors were involved in the conception of this retrospective study, in the interpretation of data, and in the writing of the manuscript.

Compliance with Ethical Standards

Ethical approval This study involved retrospective review of patient charts who had received standard management for CUP. Since patients are de-identified, and no study procedures were performed, ethical approval was not required.

Conflicts of interest Dr. Greco received honoraria for speaking engagements for BioTheranostics, Inc and serves as a consultant. BioTheranostics, Inc offers the diagnostic test CancerType ID for unclear diagnoses and was used on the patients reported in the manuscript. This test is commercially available and no funding was provided. Dr. Hainsworth has no conflicts of interest to disclose.

Funding No sources of funding were used to assist in the preparation of this study.

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